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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,659	05/11/2001	Steven M. Ruben	PZ003P4	5111

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	26

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,659	RUBEN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-35 and 56-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-35 and 56-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Non-Final Office Action is a reply to the "Response under 37 C.F.R. §1.111" filed 4 August 2003 (Paper No. 25) in response to the Non-Final Office Action mailed 3 March 2003 (Paper No. 23). Claims 24-35 and 56-75 were considered in Paper No. 23. No amendments were made to the claims in Paper No. 25. Claims 24-35 and 56-75 are pending and under consideration.

Information Disclosure Statement

In Paper No. 25, Applicant refers to several articles that are allegedly cited on an IDS. However, no IDS was filed with the Paper and the references referred to do not appear on the only IDS presently in the case (filed 15 February 2002). References cited in Paper No. 25 that have been considered by the Examiner are cited on the attached PTO-892.

Response to Arguments

Claim Rejections - 35 USC § 101

Rejection of claims 24-35 and 56-75 under 35 U.S.C. 101 is withdrawn in view of Applicant's arguments of record and the disclosures of Page *et al.* WO 01/36979 and Page *et al.* (2000) Nature 405:797-800, which teach elevation of Neurokinin B in early pregnancy is an indicator of hypertension and pre-eclampsia and that the treatment with certain neurokinin receptor antagonists may be useful in alleviating the symptoms of pre-eclampsia. Although there is no evidence to support the vast majority of utilities asserted for the claimed invention, the

post-filing art indicates that diagnosis of pre-eclampsia is a specific and substantial utility for the claimed invention.

Claim Rejections - 35 USC § 112

Claims 24-35 and 56-75 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. The grounds for the enablement rejection are explained in detail herein below and this rejection is made non-final to allow Applicant an opportunity to respond to the expanded arguments.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to an isolated protein comprising the amino acid sequence of a human preprotachykinin B and fragments thereof. As pointed out in previous Office Actions, the specification teaches the claimed polypeptides, and antibodies raised using the polypeptides, can be used for diagnosis of diseases

and conditions of the reproductive and embryonic systems (page 36). It is asserted therein that expression of the gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types and used to identify individuals having a disorder such as reproductive or embryonic disorders including pre-eclampsia.

State of the prior art and level of predictability in the art: Art published after the effective filing date of the instant application indicates that elevated levels of neurokinin B are associated with pre-eclampsia, and therefore the claimed invention is useful in development of diagnostic and/or therapeutic agents for pre-eclampsia (see especially the Page *et al.* publications cited above). However, the art also teaches that, at the time of filing, the skilled artisan would not know how to use the clamed invention, or a diagnostic or therapeutic agent developed therewith, to diagnose or treat preeclampsia without specific guidance as to how the instant neurokinin B was involved in placental blood flow in the pathological state. Page *et al.* (2000) teaches that pre- the primary vascular manifestation of pre-eclampsia is increased blood pressure. However, the art published prior to the effective filing date of the instant application is silent with regard to the involvement of tachykinins in pre-eclampsia. The relevant art also teaches that the effects of any given tachykinin on any given mammal are unpredictable. In reviewing the pharmacological actions of tachykinins, Severini *et al.* (2002) 54:285-322 teaches "[the findings discussed] demonstrate that in some mammalian species, exogenous tachykinins display a potent dilation of regional musculature accompanied by the fall of systemic blood pressure, in other mammalian and non-mammalian species the peptides display inconsistent and variable effects: hypotensive/hypertensive or even frank hypertensive responses. Thus, the intervention of endogenous tachykinins in the regulation of blood pressure and regional circulation is certainly

possible but *irregular and unpredictable*" (page 300, column 1, second paragraph). Severini *et al.* further teaches, "[i]n the intact animal, response of the vasculature to tachykinins is complex, depending upon the animal, species, density in the smooth muscle cells, and the endothelium of the different receptor types as well as the kind of tachykinins administered or released" (page 300, column 2, first full paragraph). Thus, Severini *et al.*, upon reviewing the state of the art with regard to the effects of tachykinins on the vascular system, conclude that the effect of this family of peptides is highly unpredictable, in most cases inducing vasodilation and hypotension while in some cases inducing vasoconstriction and hypertension. Based on these teachings, the skilled artisan would not know how to use a newly discovered tachykinin expressed in the placenta, or diagnostic or therapeutic agents developed therewith, to diagnose or treat preeclampsia because one of ordinary skill would not be able to predict whether the tachykinin is expressed in such a way as to contribute to the pre-eclampsia phenotype or has vasoconstrictor or vasodilator activity. Thus, the skilled artisan is dependent upon the teachings of the instant specification to describe how the claimed invention can be used to diagnose or treat preeclampsia.

Amount of direction provided by the inventor and existence of working examples: As described in previous Office Actions, the specification provides only broad general teachings that expression of the gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types and used to identify individuals having a disorder such as reproductive or embryonic disorders or cancer and suggests pre-eclampsia as one of many possible reproductive disorders that could be diagnosed or treated. However, the specification is silent with regard to whether a change in neurokinin B expression can be correlated in anyway with pre-eclampsia. Absent teachings of how neurokinin B expression is correlated with pre-

eclampsia or the role of neurokinin B in pre-eclampsia, the skilled artisan would not know how to diagnose or treat pre-eclampsia using the claimed invention or agonists or antagonists of neurokinin B. For example, the skilled artisan would not know if elevated or reduced neurokinin B expression is an indicator of a normal condition or pre-eclampsia. Likewise, the skilled artisan would not know whether the administration of an agonist or antagonist of neurokinin B would be therapeutic or injurious to a patient with pre-eclampsia.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative skill in the art is high, at the time the instant application was filed the skilled artisan would not know how to use the claimed invention to diagnose or treat pre-eclampsia without first engaging in undue empirical experimentation. The teachings set forth in the specification provide only a disclosure of a neurokinin B polypeptide and a demonstration that the polypeptide is expressed in placenta. The specification then generally teaches that the polypeptide, or other agents developed therewith, can be used to diagnose or treat conditions, including pre-eclampsia, wherein neurokinin B expression is altered. However, given the state of the art at the time of filing, the skilled artisan would not know whether neurokinin B expression is altered in pre-eclampsia or whether agonists or antagonists of neurokinin B would be effective therapeutics for treatment of preeclampsia. Therefore, the skilled artisan would have to engage in undue trial and error experimentation to establish a role for neurokinin B in pre-eclampsia such that effective diagnostic and/or therapeutic agents and procedures could be developed. As the amount of experimentation required to use the claimed invention for the purpose set forth in the specification is clearly beyond what would be considered routine in the art, the claimed invention lacks an enabling disclosure.

In response to the rejection set forth in the previous Office Action, Applicant argues that, "it was well-known in the art prior to the filing date of the instant application that members of the tachykinin family were involved in preeclampsia and pregnancy-induced hypertension" (page 2) and cites articles indicating that Substance P increases uterine blood flow in rabbits and relaxes human intramyometrial arteries and fetal stem villous arteries, and that bradykinin induces relaxation in arteries of normotensive pregnant women, and to a lesser extent, in women with preeclampsia. However, the art cited by applicant does not indicate that any tachykinin other than Substance P can regulate uterine blood flow, and certainly does not suggest that all tachykinins, or the instant claimed invention, are useful for diagnosing or treating preeclampsia or eclampsia. Furthermore, the art does not teach that neurokinin B expression is altered in pre-eclampsia or how modification of neurokinin B expression would affect the pre-eclampsia phenotype. The Hansen *et al.* reference does not suggest that tachykinins other than Substance P increase uterine blood flow and does not teach that even Substance P can be used to diagnose or treat preeclampsia or eclampsia. Knock and Poston do not even mention tachykinins as a possible mediator of the bradykinin effect, instead they attribute the effect to bradykinin stimulated nitric oxide release (see especially the left column on page 1674), and therefore clearly do not teach or suggest that any tachykinin in general or the instant claimed invention in particular can be used to diagnose or treat preeclampsia and eclampsia. Thus, the art provides only limited evidence that one member of the tachykinin family can modulate uterine blood flow, and does not teach the skilled artisan how to use the instant claimed invention to diagnose or treat pre-eclampsia.

Applicant cites several articles published well after the effective filing date of the instant application, which indicate that the claimed invention is indeed involved in preeclampsia. Applicant contends that post-filing date scientific papers may be used to corroborate Applicant's asserted utility based on *In re Brana* wherein the court found that a declaration dated after the filing date could be used to substantiate any doubts about the asserted utility. However, the facts in *In re Brana* are not analogous to the instant case. The Brana application disclosed compounds that were closely related structurally to compounds known to have antitumor activity, and asserted only that the compounds had utility as antitumor agents. In the instant case, the specification discloses a compound that is homologous to a family of peptides having disparate functions and asserts that the compound can be used to diagnose or treat a wide variety of conditions ranging from preeclampsia to Alzheimer's disease. Four years after the effective filing date of the application, the art establishes that one of the dozens of asserted utilities happens to be correct. In *Genentech Inc. v. Novo Nordisk A/S* (CA FC) 42 USPQ2d 1001 the court found, "if there is no disclosure of any starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art." In the instant case, the disclosure fails to provide basic and essential guidance as to how one of ordinary skill would be able to use the claimed invention to diagnose or treat pre-eclampsia, such as whether neurokinin B levels are altered in pre-eclampsia or whether to administer an agonist or antagonist of neurokinin B to treat pre-eclampsia. Thus, there is failure to meet the enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art.

Next, Applicant asserts that the similarity of the instant claimed invention to other Neurokinin B polypeptides indicates that it is likely to belong to the tachykinin family. Applicant asserts that simply assigning the instant polypeptide to the tachykinin family based on sequence homology, and as a human Preprotachykinin B in particular, would be sufficient to provide a well-established use for the diagnosis of pregnancy-related disorders such as preeclampsia. This argument is not found persuasive because, at the time the instant application was filed, the skilled artisan would not know how to use a protein based solely on the disclosure of it's belonging to the tachykinin family or being a Preprotachykinin B. None of the art of record published prior to the effective filing date of the instant application provides a well established utility for all polypeptides belonging to the tachykinin family or establishes how Preprotachykinin B can be used for the diagnosis or treatment of pre-eclampsia (see above).

When viewed in context, the teachings set forth in the specification amount to no more than a suggestion as to how the skilled artisan might be able to use the claimed invention to diagnose or treat pre-eclampsia with no specific disclosure of how said diagnose or treatment might be carried out. Thus, Applicant's arguments are not found persuasive individually or as a whole and the claims stand rejected under 35 U.S.C. 112, first paragraph.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

DAVID GUZO
PRIMARY EXAMINER